of heightened incentive salience to food-related stimuli is elevated intake, though consumption by itself is a downstream measure of incentive salience [5]. Future studies on the back of this pioneering report [2] will no doubt accompany 'wanting' measures of food intake with measures that better isolate incentive salience [5,12,20].

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Closed Mitosis: A Timely Move before Separation

Faithful chromosome segregation entails long-range chromosome movement into newly dividing cells. A recent study implicates CDK1 function in releasing mitotic telomeres from the nuclear envelope, thereby liberating chromosomes for mitotic segregation.

Hani Ebrahimi and Julia Promisel Cooper

In a sea of relatively free-floating nucleoplasm, the nuclear envelope (NE) provides a solid platform to which chromosomes can anchor and limit their movement [1,2]. Settling of a chromosome within its territory [3] allows the creation of distinct subnuclear microenvironments that can influence gene expression and recombination [4–6]. During mitosis, however, replicated chromosomes must be able to move freely into newly dividing cells. In many eukaryotes, the nuclear envelope (NE) is broken down prior to mitosis, allowing unhindered chromosome movement directed by the mitotic spindle. What happens in organisms that do not break down the NE prior to mitosis? A new paper by Fujita and colleagues [7] published in this issue of *Current Biology* highlights the importance of cell cycle regulated telomere detachment from the NE during the closed mitosis of the fission yeast *Schizosaccharomyces pombe*, and raises fascinating questions about the control of chromosome location in all organisms.

Telomeres are associated with the NE during interphase of the fission yeast cell cycle (Figure 1) [8,9]. By measuring the telomere-to-NE distance throughout the cell cycle, Fujita and colleagues show that fission yeast telomeres detach from the NE during early stages of mitosis and remain detached until mitotic completion. This cell cycle regulated positioning is reminiscent of the dynamics of budding yeast telomeres, which tend to attach to the NE but dislodge as cells prepare for mitosis [10,11]. The dislodgment of budding yeast telomeres occurs in late S phase and is triggered by telomeric DNA replication [12]. In contrast, fission yeast telomeres attach to the NE through G2, detaching only at early mitosis, an observation which is in keeping with experiments showing that fission yeast utilize G2/M regulation more prominently than budding yeast. This mitosis-specific telomere dislodgment points to a cell cycle regulated modification in the telomere–NE anchoring pathway.

Telomere–NE attachment is mediated by the highly conserved telomere-associated protein Rap1, which interacts with both the telomeric DNA binding protein Taz1 (ortholog of human TRF1 and TRF2) and the inner NE protein Bqt4 (Figure 1, top inset) [8]. Rap1 also functions collectively with Taz1 during other cell cycle phases, preventing chromosome end-fusions in G1 and regulating

telomere synthesis in S phase [13,14]. Since Rap1 provides the molecular link between telomeres and Bqt4, mitotic dislodgment of telomeres may be the result of loss of Rap1 function in tethering telomeres. Any mitosis-specific effect on Rap1 function could be predicted not to negatively impact telomere replication and protection, which have been already established during interphase.

Elegant experiments by Fujita and colleagues [7] show that while Rap1 levels are constant throughout the cell cycle, it is phosphorylated on five residues specifically during mitosis. A phosphatase-sensitive shift in Rap1's gel mobility was observed in M-phase of a synchronized culture, and phospho-specific antibodies specific for each of the five residues showed M-phase-specific phosphorylation. Interestingly, these phosphorylated residues localize within the Bqt4-interacting region of Rap1. In agreement with a model in which mitosis-specific phosphorylation of Rap1 prevents its interaction with Bqt4, a phosphomimetic form of Rap1 is no longer able to interact with Bqt4, as shown in two different protein interaction assays. Nonetheless, this phosphomimetic form of Rap1 can interact with Taz1. Therefore, phosphorylation of Rap1 appears to control specifically its function in telomere attachment to the nuclear envelope.

Four of the five phosphorylated residues within Rap1 lie within consensus sites for fission yeast Cdk1 (Cdc2), and mutational analysis pinpointed one of these Cdc2 consensus sites as the crucial determinant of Rap1 dissociation from Bqt4. Furthermore, this crucial residue is no longer phosphorylated in the presence of a temperature-sensitive form of Cdc2 at non-permissive temperature. This Rap1 phosphorylation at mitotic onset by the central cell cycle controlling kinase suggests CDK control of telomere release from the NE (Figure 1, bottom).

To investigate whether Cdc2-mediated Rap1 phosphorylation controls telomere release from the NE, Fujita *et al.* [7] replaced wild-type Rap1 with either a phosphomimetic (Rap1-5D and Rap1-5E) or a non-phosphorylatable (Rap1-5A) form in fission yeast cells. Cells

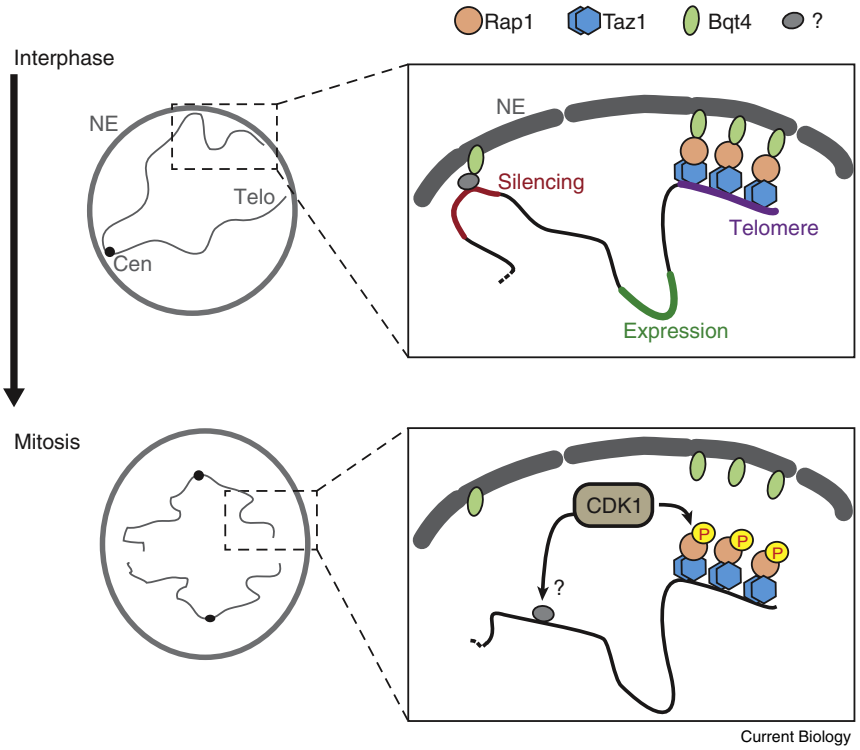

Figure 1. Cell cycle regulation of chromosome organization by CDK1.

Cell cycle regulation of chromosome organization by CDK1. During interphase, chromosomes are organised in the nucleus (top left), with telomeres and silenced chromosomal regions associating with the nuclear envelope (top right). During mitosis, however, these associations are severed (bottom left). CDK1-mediated phosphorylation may trigger the release of multiple chromosomal regions in addition to telomeres (see text for details). NE, nuclear envelope; Cen, centromere; Telo, telomere.

harboring Rap1-5D or Rap1-5E showed a constitutive increase in distance between telomeres and the NE. Therefore, phosphorylated Rap1 fails to localize telomeres to the NE during G2 phase or mitosis. In contrast, telomeres bound by Rap1-5A associate with the NE during G2 and dissociate during mitosis, showing similar mitotic movements to wild-type telomeres with the exception of a premature reassociation with the NE upon dissolution of the mitotic spindle. Hence, release of telomeres from the NE at mitosis must be conferred by additional mechanisms, possibly including spindle elongation itself, that may be redundant with Rap1 phosphorylation.

Is telomere release from the NE essential for mitosis? Fujita *et al.* [7] addressed this question using a 'forced tethering' strategy. Telomeres were artificially linked to the NE by replacing wild-type Taz1 with a fusion between Taz1 and the transmembrane domain of Bqt4, bypassing the requirement for Rap1 in the telomere–NE anchoring pathway. In these cells, mini-chromosome loss rates were higher than in wild-type cells; moreover, anaphase bridges between separating chromosomes and instances of chromosome fragmentation were observed. Mini-chromosome loss rates were reduced but still higher than wild-type rates when the Taz1 fusion protein was mutated to reduce its association with the NE. Important control experiments showed that the Taz1 fusions did not substantially disrupt its function in regulating telomere length and end protection, at least in part discounting the possibility of a Taz1-null phenotype.

The chromosome missegregation events imposed by enforcement of telomere–NE attachments occur in less than 40% of cells, suggesting that additional mechanisms may be in place to ensure faithful chromosome segregation in case of failure to dissolve telomere–NE associations. Alternatively, chromosomes that fail to

detach may segregate properly if their telomeres happen to be placed away from the plane of nuclear division; those persistent telomere–NE attachments that cause chromosome missegregation may have a higher likelihood to be positioned at the division plane.

The data presented by Fujita and colleagues [7] establish telomere detachment during mitosis as an important facet of the role of CDK1 in coordinating cell cycle progression. Recently, Steglich and colleagues [15] reported that many chromosomal loci in gene-poor regions tend to position near the nuclear envelope, and heterochromatic loci in general have been found at the nuclear envelope in many organisms [6]. Since fission yeast Rap1 is present only at telomeres, additional mechanisms may be involved in regulating the release of other chromosomal loci from the nuclear envelope, and it will be fascinating to find out whether CDK1 stimulates the release of diverse non-telomeric gene-poor regions (Figure 1, bottom inset). Repetitive and gene-poor regions represent a much larger portion of the genomes of mammalian cells and therefore it may be extremely challenging to ensure detachment of all these regions from the NE in time for mitosis. Hence, nuclear envelope breakdown, which is also regulated by CDK1, may have arisen in part as an alternative strategy to coordinate the liberation of these chromosome segments during mitosis. An important lesson may perhaps be learned from lower eukaryotes that do not undergo closed mitosis. For instance, in the yeast *Schizosaccharomyces japonicus*, the nuclear envelope is ruptured during anaphase [16] and the pathogenic fungus *Ustilago maydis* undergoes open mitosis after the nuclear envelope is ruptured [17]. It is possible that these organisms lack mechanisms that trigger chromosome detachment from the nuclear envelope and therefore rely on opening of the nuclear envelope to allow unhindered chromosome movement.

In conclusion, chromosome movement is constrained during interphase as a result of multiple associations between chromosomal regions and the NE, and these constraints allow the nucleus to encompass a range of distinct molecular environments, providing scaffolds for regulation of chromatin assembly and function. These chromosome–NE associations must, however, dissolve in time for mitosis to allow faithful chromosome segregation. The release of chromosomes from the NE during mitosis is universal among eukaryotes. How this release is ultimately achieved may vary and may depend on the size of the genome and extent of chromosome–NE associations. The report discussed here highlights the importance of CDK function for the release of telomeres. The effects of CDK activity on chromosome positioning promises to be an area of intense research in the future.

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Evolution: Remodelling Hermit Shellters

Land hermit crabs hollow out the shells in which they live. A new study shows that remodelled shells afford better survival, with important implications for sociality and evolution.

Geerat J. Vermeij

No, there's no typo in the title: hermit crabs really do live in 'shellters' — the shells of snails they occupy after the original builders have died; so, these portable houses — one for each crab — are appropriately referred to as 'shellters'. Land living hermit crabs of the genus *Coenobita* are unique among the thousands of otherwise mostly marine hermit-crab species in that they hollow out the inside of their abodes, transforming a spiral cavity into a more